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(54) Water-soluble benzothiazine dioxide salts.

(57) The water-soluble lysine and arginine salts of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1,-dioxide have been prepared. These novel salts are useful in therapy as non-steroidal anti-arthritis agents, especially when administered by the parenteral route. Methods for preparing these salts from the corresponding acidic starting material and the appropriate amine base are provided.

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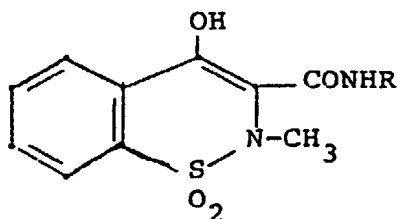
WATER-SOLUBLE BENZOTHAZINE DIOXIDE SALTS

This invention relates to new and useful benzothiazine dioxide salts. More particularly, it is concerned with certain novel water-soluble salts of N-(2-pyridyl)-
5 2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide
1,1-dioxide, which are of especial value in view of
their unique chemotherapeutic properties.

In the past, various attempts have been made
to obtain new and better anti-inflammatory agents.
10 For the most part, these efforts have involved the
synthesis and testing of various steroidal compounds
such as the corticosteroids or non-steroidal substances
of an acidic nature such as phenylbutazone, indomethacin
and the like, including a new agent known as piroxicam.
15 The latter substance is a member of a class of
anti-inflammatory 4-hydroxy-2H-1,2-benzothiazine-3-
carboxamide 1,1-dioxides described and claimed in
U.S. Patent No. 3,591,584. However, in the continuing
search for improved anti-inflammatory agents, there
20 is a definite need for anti-arthritic agents that are
adapted for parenteral administration.

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In accordance with the present invention, it has now been found that certain novel water-soluble base salts of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide are useful as non-steroidal
5 therapeutic agents for alleviating painful inflammatory conditions such as those caused by rheumatoid arthritis, for example. The novel salts of this invention are selected from the group consisting of the lysine and arginine salts of N-(2-pyridyl)-2-methyl-4-hydroxy-
10 2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, which is an acidic compound of the formula:



wherein R is 2-pyridyl. These salts are useful in alleviating the aforementioned arthritic effects, especially when given by the parenteral route of
15 administration.

In accordance with the process employed for preparing the novel salts of this invention, N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide is contacted with at least
20 an equivalent amount in moles of an organic amine base selected from the group consisting of lysine and arginine. This reaction is normally carried out in a polar protic solvent like water or a lower alkanol such as methanol, ethanol or isopropanol, etc. In general,
25 the reaction is conducted at a temperature that is in the range of from about 20°C up to about 100°C for a

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period of about one-half to about 30 minutes, although it is usually most convenient in practice to conduct the reaction at the reflux temperature of the solvent. Upon completion of the reaction, the desired salt product is easily isolated in a conventional manner, e.g., by first evaporating the solvent from the reaction mixture, followed by trituration of the resulting solid residue or crude concentrate product with a suitable solvent system such as ethyl acetate/chloroform, etc. Alternatively, it is also possible to avoid the need for isolation by employing aqueous solutions of the salt as formed in situ by appropriate adjustment in concentration of the solution.

The starting materials required for preparing the novel salts of this invention are all known compounds. For instance, N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (piroxicam) is described in U.S. Patent No. 3,591,584 to J. G. Lombardino, as well as in the paper of J. G. Lombardino et al., appearing in the Journal of Medicinal Chemistry, Vol. 16, p. 493 (1973), including its overall synthesis from readily available organic materials. The amine bases employed to prepare the novel amine addition salts of this invention are all commercially available materials.

The N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide salts of the present invention are readily adapted to therapeutic use as anti-arthritic agents. For instance, the lysine and arginine salts of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide exhibit anti-inflammatory

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activity in the standard carrageenin-induced rat foot edema test [described by C. A. Winter et al., Proc. Soc. Exp. Biol. Med., Vol. 111, p. 544 (1962)]. The herein described benzothiazine dioxide salts exhibit additional advantages. For instance, even though N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (piroxicam) per se is very poorly water-soluble, the lysine and arginine salts of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide are readily flash soluble (i.e., instantaneously soluble) in said solvent and therefore are more rapidly absorbed into the blood stream upon oral administration than the corresponding less soluble calcium salt or even the anhydrous sodium salt of said particular drug (both of which are prepared according to the procedure already set forth in U.S. Patent No. 3,591,584). Additionally, these particular salts afford water-clear, stable aqueous solutions even at very high concentration levels (> 50 mg./ml.). This is a truly surprising fact when one considers that the tromethamine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide and the corresponding triethanolamine salt are both poorly water-soluble and that the simple ammonium salt is found to be highly unstable when subjected to drying conditions under vacuum.

The herein described salts can be administered as anti-arthritis agents via either the oral, parenteral or topical routes. In general, these salts will be administered in doses ranging from about 5.0 mg. up to about 1000 mg. per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. A dosage level that is in the

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range of from about 0.08 mg. to about 16 mg. per kg of body weight per day is usually preferred, although variations may occur depending upon the individual response to said medicament, as well as on the type of pharmaceutical formulation and the time intervals at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be adequate, while in other cases higher levels may be employed, divided into several smaller doses for administration throughout the day.

The salts of this invention may be administered alone or in combination with pharmaceutically acceptable carriers by the various routes previously indicated, in a wide variety of dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, soft and hard lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, pastes, lotions, ointments, aqueous solutions and suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the salts of this invention are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato

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or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in hard geletin capsules; preferred materials also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous solutions and suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of these amine salts in sesame or peanut oil or in aqueous propylene glycol or aqueous ethanol may be employed, as well as sterile aqueous solutions in distilled water. The aqueous solutions should be suitably buffered (pH 8) and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intramuscular and subcutaneous injection purposes. Additionally, it is also possible to administer the aforesaid amine addition salts topically when treating inflammatory conditions of the skin or eye by way of creams, jellies, pastes, ointments, solutions and the like, in accordance with standard pharmaceutical practice.

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The anti-inflammatory activity of the compounds of the present invention is demonstrated in the previously mentioned standard carrageenin-induced rat foot edema test. In this test, anti-inflammatory activity is determined as the percent inhibition of edema formation in the hind paw of male albino rats (weighing 150-190 g.) in response to a subplantar injection of carrageenin. The carrageenin is injected as a 1% aqueous suspension (0.05 ml.) one hour after oral administration of the drug, which is normally given in the form of an aqueous solution. Edema formation is then assessed by measuring the volume of the injected paw initially as well as three hours after the carrageenin injection. The increase in volume three hours after carrageenin injection constitutes the individual response. Compounds are considered active if the difference in response between the drug-treated animals (six rats/group) and a control group receiving the vehicle alone is significant on comparison with the results afforded by standard compounds like acetylsalicylic acid at 100 mg/kg or phenylbutazone at 33 mg/kg, both by the oral route of administration.

EXAMPLE 1

In a 1000 ml. Erlenmeyer reaction flask equipped with magnetic stirrer and reflux condenser, there were placed 3.5 g. (0.0105628 mole) of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, 1.54 g. (0.0105628 mole) of L-lysine (available from the Aldrich Chemical Company, Inc., Milwaukee, Wisconsin) and 700 ml. of ethanol to form a yellow suspension. The latter suspension was then heated to reflux and treated with 10 ml. of water which was added slowly at the reflux point. The resulting yellow

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solution was then cooled to room temperature ($\sim 25^{\circ}\text{C}.$) and evaporated to near dryness while under reduced pressure to afford a yellow foam. The latter material was subsequently treated with 400 ml. of diethyl ether by slurrying overnight for a period of approximately 16 hours and then filtered in the usual manner to give a fine yellow solid. In this way, there were ultimately obtained 4.5 g. (89%) of the pure amorphous L-lysine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (as the hemihydrate with 0.25 mole of diethyl ether). The pure product was characterized by means of mass spectroscopy and infrared absorption spectra, in addition to elemental analysis.

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4\text{S} \cdot \text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \cdot 0.5\text{H}_2\text{O} \cdot 0.25\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$: C, 52.31; H, 6.08; N, 13.86. Found: C, 52.52; H, 6.14; N, 13.77.

EXAMPLE 2

To a suspension of 5.0 g (0.0151 mole) of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide in 400 ml of water, there were added 2.77 g (0.0159 mole) of L-(+)-arginine (available from Fisher Scientific Company, New York, N.Y.) and the resulting mixture was heated on a steam bath, with stirring, for a period of five minutes. The aqueous solution so obtained was then filtered to remove some minor insolubles, followed by concentration of the resulting filtrate in vacuo to yield a yellow oil as the residual liquid. Trituration of the latter material with a chloroform (80 ml)/ethyl acetate (150 ml) solvent system, followed by stirring at room temperature ($\sim 25^{\circ}\text{C}$) overnight (~ 16 hours) under a dry nitrogen atmosphere then gave a yellow solid precipitate which was

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subsequently recovered by means of suction filtration. After drying the recovered solid material in vacuo at 57°C (1.0 mm Hg) to constant weight, there was ultimately obtained a 5.36 g (70%) yield of the pure amorphous L-arginine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (as the hydrate), mp 142-145°C (decomp.). The pure product was further characterized by means of elemental analysis.

Anal. Calcd. for $C_{15}H_{13}N_3O_4S \cdot C_6H_{14}N_4O_2 \cdot H_2O$: C, 48.17; H, 5.58; N, 18.73. Found: C, 47.84; H, 5.72; N, 18.69.

EXAMPLE 3

An aqueous injectable solution is prepared by first intimately admixing one part by weight of the L-lysine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide with 2.5 parts by weight of disodium phosphate with the aid of a mortar and pestle. The ground dry mixture so obtained is then sterilized with ethylene oxide and thereafter aseptically placed into vials and sealed. For purposes of intravenous administration, a sufficient amount of distilled water is added to each of the filled vials before use so as to ultimately provide a solution which contains 10 mg. of the active ingredient per each ml. of injectable solution.

CLAIMS

1. The lysine or arginine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide.
2. A compound as claimed in claim 1 which is the lysine salt.
3. A compound as claimed in claim 1 which is the arginine salt.
4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a salt as claimed in any one of claims 1 to 3.
5. A compound as claimed in any one of claims 1 to 3 for use in treating an arthritic condition in a human being.

CLAIMS FOR AUSTRIA

1. A process for preparing a water-soluble lysine or arginine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, characterized by reacting N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide with lysine arginine.

2. A process as claimed in claim 1, characterized by the fact that at least an equivalent amount in moles of lysine or arginine is employed with respect to the N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

3. A process as claimed in claim 1, characterized by the fact that said reaction is carried out in a polar protic solvent.

4. A process as claimed in claim 3, characterized by the fact that said solvent is water.

5. A process as claimed in claim 3, characterized by the fact that said solvent is a lower alkanol.

6. A process as claimed in claim 1, characterized by the fact that said reaction is conducted at a temperature that is the range of from about 20°C. up to about 100°C.

7. The process as claimed in claim 1 wherein the lysine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide is prepared.

8. The process as claimed in claim 1 wherein the arginine salt of N-(2-pyridyl)-2-methyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, is prepared.



European Patent
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EUROPEAN SEARCH REPORT

0066458

Application number

EP 82 30 2728

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
A	US-A-4 074 048 (H. ZINNES) * Columns 6,7; example 8 * -----	1	C 07 D 417/12 A 61 K 31/54
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 D 417/00 C 07 D 279/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 01-09-1982	Examiner CHOULY J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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